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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,496	06/09/2006	Dirk Finsinger	MERCK-3171	2879

23599 7590 12/12/2007

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,496	FINSINGER ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,19-28,30,31 and 33-47* is/are pending in the application.

4a) Of the above claim(s) *11-13,15,19-28,30,31 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14,36-39,43 and 47* is/are rejected.

7)☒ Claim(s) *40-42 and 44-46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12 June 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/12764 filed 11/11/2004 which claims priority to EP 03028268.5 filed 12/10/2003.

Claims 1-15, 19-28, 30-31, 33-47 are pending. Claims 1-10, 14, 36-47 are under examination. Claims 11-13, 15, 19-28, 30-31, 33-35 are withdrawn from consideration.

Response to Restriction/Election

2. Applicant's election with traverse of Group I and the species of example 44, in the reply filed on November 26, 2007 is acknowledged. The traversal is on the ground(s) that it was improper because subject matter was excluded and that a Lack of Unity was not found since the reference cited by the examiner was not anticipatory. With respect to the later, the examiner apologizes for this clear oversight, and now applies the Aldrich Chemical catalog 1992 pg. 124 "Benzoic hydrazide" CAS No. 613-94-5, reading on claim 34, where Y is O, Ar1 is phenyl, and R8 is H as a reference showing lack of unity. This compound appears to read on the claim, as no proviso can seem to be found and this claim is independent. This "Benzoic hydrazide" Markush alternative of claim 34 is not novel, so no special technical feature is present. The applicant is incorrect that some subject matter was excluded, since Group III previously contained all material not in groups I-II, nonetheless some new groups have been added to prevent confusion. The examiner failed to understand the meaning of claims 34 and 35. Since both claims were previously dependent on claim 3 it was naturally assumed that they would correspond to a subgenus of compounds of claim 3. The examiner hereby creates three new groups corresponding to claims 34, 35, and other subject matter not included in groups I-III. The examiner believes that such a grouping now accounts for all subject matter, however should the

applicant disagree he/she is invited call the undersigned to discuss. Please note that the new claims including the "use" claims converted to method claims have been given an appropriate grouping. The final compound group, Group VI, contains all material not included in groups I-V (subject to further restriction). Also note that claim 13 is withdrawn form consideration as it is drawn to multiple ingredient pharmaceutical compositions, and which are compounds of unknown structure ("additional compounds"). The examiner had previously made reference to pending rules changes regarding the number of claims, in light of the preliminary injunction awarded to GSK, such reference is hereby withdrawn. This application contains claims drawn to a nonelected invention with traverse. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Group I, Claims 1-10, 14, 36-47 drawn to compounds and compositions reading on D is a "bivalent diacyl hydrazine", A is $-L(M\text{-}L')_\alpha$ where L is a phenyl, L' is pyridine, M is a bond or oxygen, B is a phenyl drawn to dibenzoyl-pyridinyl-hydrazines, shown as Group **I** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group II, Claims 1-10, 14, 36-47 drawn to compounds and compositions reading on D is a "bivalent diacyl hydrazine", A is $-L(M\text{-}L')_\alpha$ where L is a phenyl, L' is phenyl, M is a bond or oxygen, B is a phenyl drawn to dibenzoyl-phenyl-hydrazines, shown as Group **II** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group III, Claims 1-10, 14, 36-47 drawn to compounds and compositions reading on D is a "bivalent diacyl hydrazine", A is $-L(M\text{-}L')_\alpha$ where L is a phenyl, L' is pyridine, M is a bond or oxygen, B is indole drawn to benzoyl-indolyl-hydrazines, shown as Group **III** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group IV, Claim 34, drawn to compounds and compositions reading on Formula III. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election will be made.

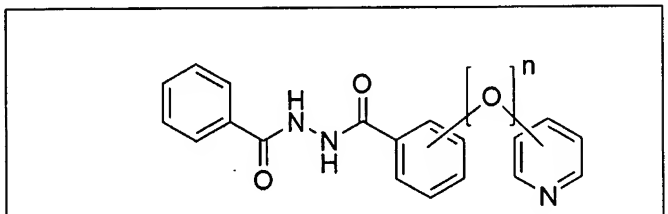
Group V, Claim 35 drawn to compounds and compositions reading on Formula IV. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election will be made.

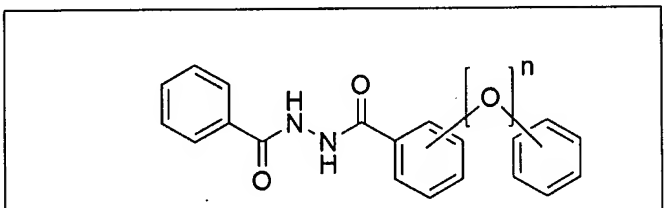
Group VI, Claims 1-10, 13, 14, 36-47 drawn to compounds and compositions not encompassed by Groups I-V. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election will be made.

Group VII, Claims 15, 33 drawn to methods of making the compounds and compositions of a group I-VI (limited in scope to a single group). If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the species election will be required.

Group V, Claims 11, 12, 19-28 30-31, drawn to methods of preventing or treating various diseases or conditions, limited in scope to one of the compounds of groups I-VI. If this group is elected, a single disclosed species of compound in addition to a single disease or disorder is also required. Further restriction based on the election will be made.

Figure 1 has been provided to the applicant to aid in the election:





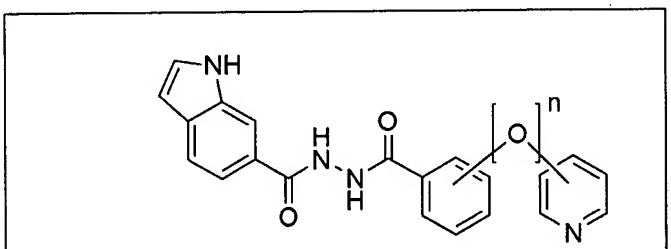


Figure 1. Groups I - III.

The inventions listed as Groups I-V do not relate to a single general inventive concept under 35 USC 121 or PCT Rule 13.1 because:

PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

PCT Rule 13.2 states that the unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Annex B, **Part 1(a)**, indicates that the application should relate to only one invention, of if there is more than one invention, inclusion is permitted if they are so slinked to form a single general inventive concept.

Annex B **Part 1(b)**, indicates that "special technical features" means those technical features that as a whole define a contribution over the prior art.

Annex B **Part 1(c)**, further defines independent and dependent claims. Unity of invention only is concerned in relation to independent claims. Dependent claims are defined as a claim that contains all the features of another claim and is in the same category as the other claim. The category of a claim refers to the classification of claims according to subject matter e.g. product, process, use, apparatus, means, etc.

Annex B **Part 1(e)**, indicates that the permissible combinations of different categories of claims. **Part 1(e)I**, states that inclusion of an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product is permissible.

Annex B, **Part 1(f)**, indicates the "Markush practice" of alternatives in a single claim. **Part 1(f)I**, indicates the technical relationship and the same or corresponding special technical feature is considered to be met when (A) all alternatives have a common property or activity, and (B) a common structure is present or all alternatives belong to a recognized class of chemical compounds. Further defining (B), Annex B, **Part 1(f)(i-iii)**, the common structure must; a) occupy a large portion of their structure, or b) the common structure constitutes a structurally distinctive portion, or c) where the structures are equivalent and therefore a recognized class of chemical compounds, each member could be substituted for one another with the same intended result. That is, with a common or equivalent structure, there is an expectation relationship and the corresponding special technical feature result from a common (or equivalent) structure that is responsible for the common activity (or property). **Part 1(f) iv**, indicates that when all alternatives of a Markush grouping can be differently classified, it shall no, take alone, be considered justification for finding a lack of unity. **Part 1(f)v**, indicates that
"When dealing with alternatives, if it can be shown that at least *one* Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner"

In the instant case, at least one Markush alternative is not novel because prior art by Aldrich Chemical Company Catalog 1992 pg. 124 "Benzoic hydrazide" CAS No. 613-94-5, reading on claim 34, where Y is O, Ar1 is phenyl, and R8 is H, thus the lack of a special technical feature is apparent.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The object A-D-B has no clear meaning in chemistry and is not art recognized. While applicant can be his or her own lexicographer, the applicant is attempting to be his or her own semiotician and it is not clear how these representations of the applicant would translate into something of actual chemical meaning. Applicant's chemical semiotics are such that no chemist would ascertain what these symbols and definitions mean. See Jones, Maitland *Organic Chemistry* Norton: New York, 1997, pg. 84-99, in his discussion of Newman projections at pg. 84 paragraph 3, line 3, "Like all devices, it contains arbitrary conventions, which can only be learned, not reasoned out...." and at page 99, discussing organic structural representation in general "there is a tension between our need to talk quickly and efficiently to each other and the accurate representation of these complicated organic structures. The tension is at least partly resolved by using codes, but the price of this use is that you *always* must be able to see past the code to the real, three dimensional structure....." What convention is being used in Formula I? Where are the rules for learning this convention? It appears that D is a "diacyl hydrazine moiety", yet the term "acyl" is indefinite. There is no one, generally accepted, definition of acyl. Furthermore the claims recite "derivative thereof". The term derivative has no meaning unless one specifies the method of derivation. What is the method of derivation being used here? It is unclear what "a carbon based moiety" encompasses. The examiner has tried his best to examine these representations, however in some cases where in Formula I there is no variable due to the restriction requirement the structure should be amended to reflect this meaning and the actual

structure be drawn in some conventional manner to clearly point out and distinctly describe the invention. See MPEP 2173.05(m) for guidance regarding prolix.

4. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to compounds, despite the recitation of functional language "medicament". Functional language as that of the instant claims carries no patentable weight in claims for compositions of matter see *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 where "composition claims cannot, as the appellant refiners argue, embrace only certain uses of that composition. (citing In Re Spada) Otherwise these composition claims would mutate into method claims." It is unclear if this is a method claim or a compound claim. It is recommended that this claim be rewritten to reflect to remove intended use.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, 10, 14, 36-39, 43, 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows:

The variables in claim 6, with a definition of R^9 as H. In addition enablement on R^8 has been provide for O-alkyl-NH_2, and S-alkyl.

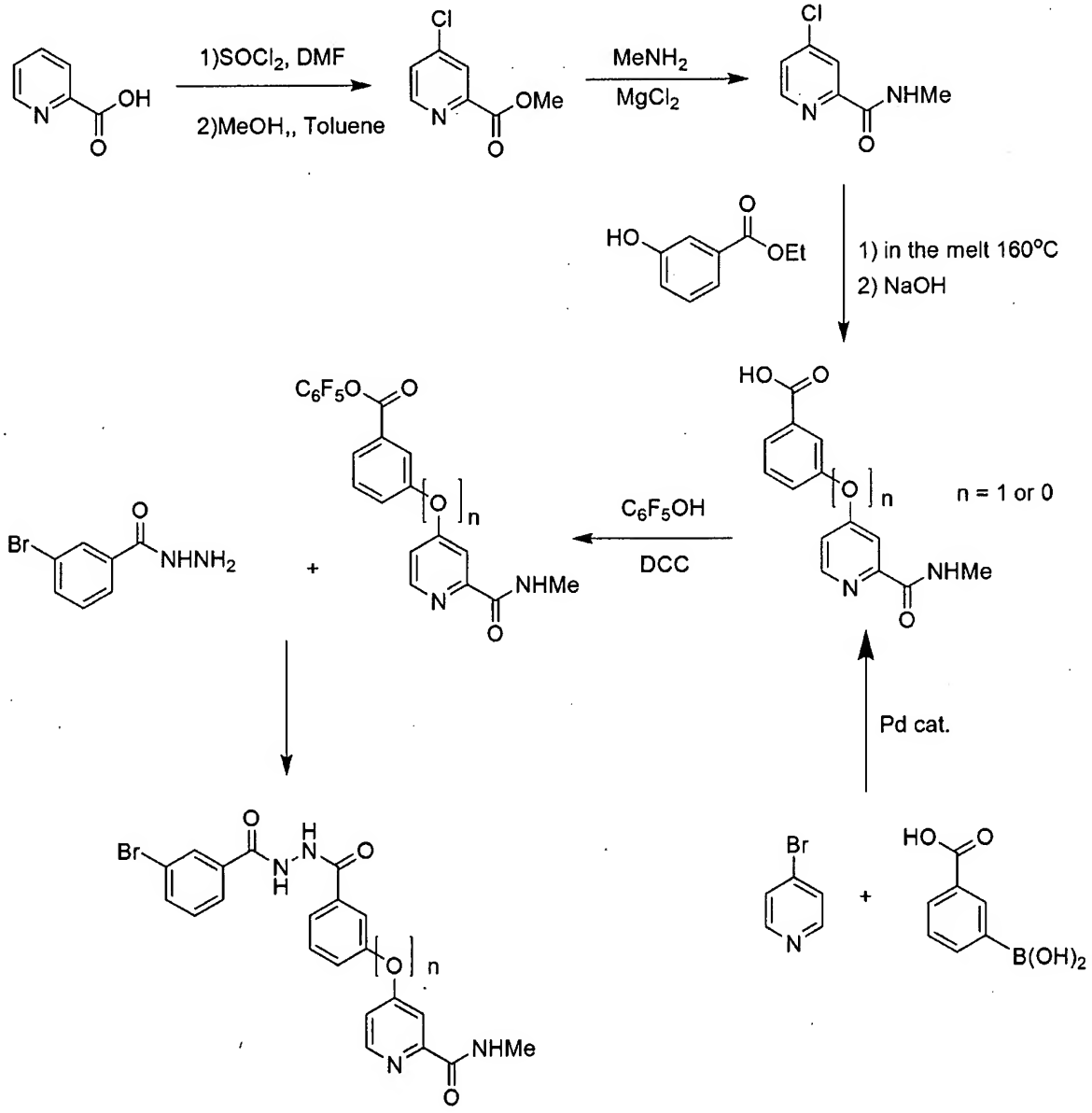
The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all known chemical structures and heretofore unknown groups defined only by number atoms, the size of a ring (claim 1), and other groups bearing multiple substitutions of undefined structure "a carbon based moiety" **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as a raf kinase inhibitor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (C, E-H) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed

directly after such a remark or explication. The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the chemistry required to prepare the compounds. The only example given is that of pgs. 157-161, reproduced in Scheme 1.



Scheme 1. Synthesis of the compounds of the instant case.

The chemistry used to construct the compounds is not applicable to the scope claimed and currently no methods exist for the scope claimed. The limitations of synthetic chemistry are readily apparent as stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures

> [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. **(E)**

The reaction of phenols with bromopyridine to yield the phenyl-pyridyl ethers has several limitations as to what substituents are tolerated. The substituents on the phenol should be electron rich if it is *ortho* or *para* to the phenol oxygen, and the bromopyrdines should possess electron withdrawing groups (see March, J. *Advanced organic chemistry*, **1985**, 589). It is somewhat surprising that other halogens are claimed, as the other halogens are well known to react in such reactions (see March, J. *Advanced organic chemistry*, **1985**, 589). The most disturbing examples in the instant case are listed as alkylhalide on R8, which will give cyclic ethers via the well known Williamson ether synthesis March pg. 342-343. In addition alkynes and alkenes will undergo addition of phenol as is well known (March *Advanced organic chemistry* pg. 684-685.) If this alkyne is terminal it will be deprotonated and undergo subsequent reaction with other electrophilic groups. Intramolecular cyclization of the phenol oxygen onto pendant olefins and alkynes in the ortho position as is well known in the art. Hurd

et. al. *J. Am. Chem. Soc.* **1940**,*5*, 212-222, entire document) teach that olefins react to give chromans (applicant heats the reaction to 160°C in subsequent steps). Buckle et. al *J. Chem. Soc. Perkin Trans. 1* **1985**, 2443-2446 entire document, teaches that phenolate anions with pendant alkynes will produce benzofurans.

The synthesis of the pyridyl-phenyl moiety via the Suzuki-coupling is likewise limited. It is well known in the art that Pd undergoes oxidative addition to "halo" a substituent (readily to I, and Br), which is recited for numerous variables. The applicant's own disclosure is shown as evidence of this fact. One reviewer has made the following statement about Pd-cataylzed cross-couplings:

> The large number of highly diverse examples of high-yielding Pd-catalyzed organic reactions might give the non-specialist the impression that almost any conceivable transformation might work in the presence of a suitable Pd catalyst. This is, of course, not true, and even the most robust Pd-catalyzed processes have their limitations. Some of these will be discussed in the following sections. The most important unwanted processes which can compete with Pd(0)-catalyzed C-C bond formation include homocoupling or reduction of the halide and homocoupling, C-protonation, or oxidation of the organometallic reagent. (Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim Chapter 8, pgs. 279-308.)

Dorwald has numerous references to reactions that do not work. In particular in the instant case the claims are directed to groups of the instant case that will result in undesired processes that do not lead to the product. When a substituent is alkyl and ortho to bromo, a variety of cylcometallation process can occur and "give rise to unexpected products or, if the palladacycles are too stable, the catalyst will be consumed and no further reaction will occur." (Dorwald ibid. pgs. 298-299). In addition certain ortho groups will chelate the metal and prevent reaction: "Accordingly, aryl halides with strongly chelating ortho-substituents will undergo transition metal-catalyzed C-C bond formation only sluggishly or not at all." (Dorwald ibid. 300-301). It

is also a well known limitation of Pd catalyzed reactions that sterically bulky substituents hinder or completely inhibit the reaction.

Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald ibid. pg. 41 "It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly..." **(C & E)**

See I*n re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how compounds with these vast substituents are to be obtained. Where may the directions to prepare or buy them be found? **(F)**

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-yl-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method

of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

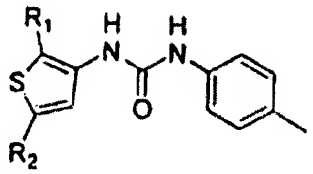
While these chemical limitations are significant, even more significant are the limitations of activity at raf kinase. What are the important structural features for the claimed utility? (The medicinal chemistry of raf kinase inhibitors is relatively well-developed and many limitations are well known in the art. It is sensitive to structural changes that may be relatively minor in the chemical sense see Timothy B. Lowinger, Bernd Riedl, Jacques Dumas and Roger A. Smith "Design and Discovery of Small Molecules Targeting Raf-1 Kinase" *Current Pharmaceutical Design*, 2002, 8, 2269-2278 2269,

"Initial medicinal chemistry efforts indicated that variation of substituents on the phenyl group in **4** had the potential to provide significant optimization of inhibitor potency (Table 1) [21, 22]. At the *para* position, small lipophilic substituents such as methyl and chloro provided an increase in potency (**5**, **6**); however, **a size limitation was revealed, as this improvement was lost with substituents having greater steric bulk** (e.g., **11–13**)..... Structure–activity trends were similar to those observed in the phenyl series, as the best analogs in this sub-class were substituted with small lipophilic groups (i.e., 30–32)." Pg. 2270

Indeed it is clear that if a substituent that is too large, or not lipophillic enough, this leads to compounds with no activity. Compound **87** which differs from compound **77** only by the substitution of phenyl for isopropyl was devoid of activity. The relevant portion of Table 3 from Lowinger et. al. is reproduced below for convenience.

2272

Table 3. Replacements for the Thiophene Substituents in 5

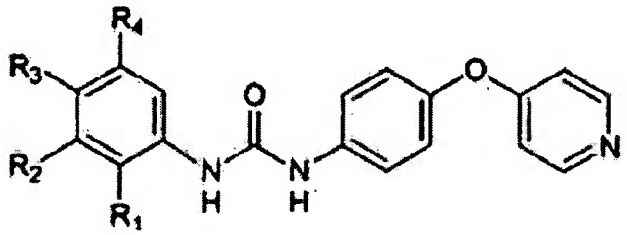


Compounds	R_1	R_2	Raf-1 kinase % inh. (25 μM)	Raf-1 kinase IC_{50} (μM)

77	$COOCH_3$	iPr		4.0
87	$COOCH_3$	Ph	0	

Moving closer to the compounds of the instant case bearing a pyridyloxy linkage to the phenyl group as in Table 11 of Lowinger et. al. While only limited information regarding a relatively small group of lipophillic substituents is available, minor changes result in markedly different activity (see the movement of the position of a chlorine atom **155** vs. **158**).

Table 11. SAR of Diphenyl Ureas Derived from the 4-(4-pyridyl-oxy)Aniline Side-chain



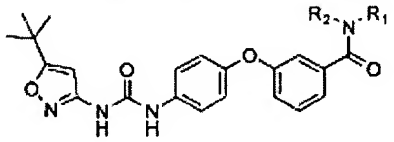
Compound	R_1	R_2	R_3	R_4	Raf-1 IC_{50} (nM)
155	H	H	Cl	CF_3	46
156	H	CF_3	H	CF_3	600
157	OCH_3	Cl	H	H	2,700
158	Cl	H	H	CF_3	450
159	H	H	H	CF_3	460
160	OCH_3	H	NO_2	H	4,400
161	F	H	H	CF_3	720
162	H	OCH_3	H	CF_3	510
163	H	H	H	OCF_3	440
164	H	H	Br	CF_3	35
165	H	H	F	CF_3	530
166	H	H	Cl	Br	450
167	OCH_3	H	Cl	CF_3	29

Moreover compound 119 of Lowinger et. al. is devoid of activity, yet the chemical change is relatively modest:

"The urea moiety clearly appeared essential for kinase inhibitory activity. Both *N*-Me derivatives **116** and **117**, as well as the cyclic urea derivative **118**, showed a dramatic loss of activity. Similarly, exchange of one nitrogen atom for a carbon as in amide **119** also resulted in a completely inactive compound."

It is apparent that caroboxamides are a preferred substituent, however it is far from clear what the effects of substitution on the carboxamide moiety is. Indeed secondary amides seem to be disfavored, based on the prior art teaching of Uday R. Khire et. al. "Omega-carboxypyridyl substituted ureas as Raf kinase inhibitors: SAR of the amide substituent." *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 783–786. A relatively minor change of H to methyl results in a 50 fold decrease in activity, see Table 1 compound **2** vs. compound **8**, (R1). Table 1 of Khire is shown below:

Table 1. Substitution of the carboxamide group



Compd	R_1	R_2	Raf-1 kinase IC_{50} (nM)[9]
2	H	Me	120
6	H	Et	130
7	H	*n*-Pr	140
8	Me	Me	5800
9	H	CH_2Ph	460
10	H	Ph	370
11	H	3-Pyridyl	68

It is clear that substituents are chosen rationally based on scientific reasoning not capriciously, see the footnote on pg. 2778, ref. 12.

"12 "Building blocks were selected 'manually' with the objective of achieving a balance of structural diversity and similarity to the hit **2**. These building blocks included a total of 75 isocyanates and ca. 300 amines, including some custom-prepared compounds. About 1500 syntheses were attempted, and ca. 1000 products were obtained having purities of >60% (HPLC, 254 nm) and confirmed identities (LC/MS).[10a] These 1000 products were submitted for testing, and keyactives that were identified were resynthesized, purified, characterized, and re-tested."

In the instant case, the amount of information provided with respect to which substituents are required for activity is noticeable absent. In fact the specification is devoid of any data regarding

the activity of the compounds. **(F & G)** In this case these compounds bear a remarkable structural resemblance to one another, yet the claims are not commensurate in scope. Based on the state of the prior art, the claims of the instant case are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only very few working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

6. Claims 1-4, 9, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue

experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims. g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed

invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Objections

7. Claims 40-42, 44-46 are objected to for depending from a rejected base claim, but would be allowable if put in proper dependent format.

8. Claim 9 is objected to for failing to list the compounds but instead has referred to the tables in the specification. A claim may not depend from the specification, but rather should be self-contained.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER

12/6/07